The COVID-19 Treatment Guidelines Panel's Statement on Anticoagulation in Hospitalized Patients With COVID-19

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Background

COVID-19 has been associated with inflammation and a prothrombotic state accompanied by increases in fibrinogen and D-dimer.[1,2] In some studies, elevations in these markers have been associated with worse clinical outcomes.[3,4] Hospitalized patients with COVID-19 are at high risk for venous thromboembolism (VTE).[5] At a minimum, hospitalized COVID-19 patients should receive prophylactic doses of anticoagulants, such as low molecular weight heparin (LMWH) or unfractionated heparin, for the duration of their hospitalization.

Recommendations

Based on the collective data from randomized controlled trials on the use of anticoagulation in patients with COVID-19, the COVID-19 Treatment Guidelines Panel (the Panel) provides the following recommendations.

For Hospitalized, Nonpregnant Adults Who Require Low-Flow Oxygen and Are Not Receiving Intensive Care Unit Level of Care

- The Panel recommends using **therapeutic-dose heparin** for patients who have a D-dimer above the upper limit of normal (ULN), require low-flow oxygen, and have no increased bleeding risk **(CIIa)**. LMWH is preferred over unfractionated heparin.
  - Based on clinical trial exclusion criteria, contraindications for therapeutic anticoagulation for COVID-19 due to an increased bleeding risk are as follows: platelet count <50 x 10^9/L, hemoglobin <8 g/dL, need for dual antiplatelet therapy, known bleeding within the last 30 days requiring an emergency room visit or hospitalization, known history of a bleeding disorder, or an inherited or active acquired bleeding disorder.
- In patients without a VTE who are started on therapeutic-dose heparin, treatment should continue for 14 days or until hospital discharge, whichever comes first.
- The Panel recommends using **prophylactic-dose heparin** (LMWH or unfractionated heparin) for patients who are not administered therapeutic heparin unless a contraindication exists **(AIIb)**.
- The Panel **recommends against** the use of **therapeutic-dose oral anticoagulants** for VTE prophylaxis or prevention of COVID-19 progression in hospitalized patients, except in a clinical trial **(AIIa)**.

For Hospitalized, Nonpregnant Adults Who Are Receiving Intensive Care Unit Level of Care (Including Patients Who Are Receiving High-Flow Oxygen)

- The Panel recommends using **prophylactic-dose heparin** as VTE prophylaxis unless a contraindication exists **(AI)**.
- The Panel **recommends against** the use of **intermediate-dose** (e.g., enoxaparin 1 mg/kg daily) and **therapeutic-dose anticoagulation** for VTE prophylaxis, except in a clinical trial **(BI)**.
- For patients who start on therapeutic-dose heparin while on low-flow oxygen due to COVID-19 and then transfer to the intensive care unit (ICU), the Panel recommends switching from therapeutic to **prophylactic-dose heparin** unless a VTE is confirmed **(BIII)**.

For Hospitalized Pregnant Adults

- The Panel recommends using **prophylactic-dose anticoagulation** for pregnant patients hospitalized for manifestations of COVID-19 unless otherwise contraindicated (see below) **(BIII)**.
- Because pregnant patients have not been included in most clinical trials evaluating therapeutic anticoagulation in the setting of COVID-19, there is currently insufficient evidence to recommend either for or against therapeutic anticoagulation for pregnant patients with COVID-19 in the absence of a known VTE.[2]

Rationale

Several randomized controlled trials have evaluated the role of therapeutic doses of heparin in reducing VTE events or mortality in patients hospitalized for COVID-19. In the ICU setting, these studies showed that therapeutic heparin did not reduce mortality but may have a higher risk of bleeding events; therefore, this approach **is not recommended**.[6]

Three open-label randomized controlled trials (a large multiplatform trial and the smaller RAPID and HEP-COVID trials) compared therapeutic doses of heparin to prophylactic or intermediate doses of the anticoagulant in selected hospitalized patients who did not require ICU care. The entry criteria for these studies varied, but typically they included need for supplemental oxygen, elevated D-dimer level, and no risk of major bleeding event. In the larger multiplatform trial, therapeutic heparin showed an increase in organ support-free days but no difference in mortality or length of hospitalization compared to prophylactic heparin.[7] The RAPID trial enrolled patients with elevated D-dimer levels and hypoxemia. The patients were randomized to receive therapeutic or prophylactic doses of heparin. There was no statistically significant difference between the arms for the primary outcome, a composite of ICU admission, noninvasive or invasive ventilation, or death at Day 28, but therapeutic heparin reduced mortality at 28 days, a secondary outcome.[8] The HEP-COVID trial enrolled patients who required supplemental oxygen and had a D-dimer >4 times ULN or a sepsis-induced coagulopathy score of ≥4. The occurrence of the primary outcome of VTE, arterial thromboembolism, or all-cause death at Day 30 was significantly lower in the therapeutic LMWH arm than in the prophylactic LMWH arm, but there was no difference in mortality at Day 30 between the arms.[9] Results from smaller randomized trials, single-center studies, and observational studies have also been published.

Based on the available study data, the Panel recommends using **therapeutic-dose heparin** for patients who have a D-dimer above the ULN, require low-flow oxygen, and have no increased bleeding risk **(CIIa)**. The rating reflects the fact that, although the 3 randomized controlled trials showed benefit of therapeutic heparin in hospitalized patients, their inclusion criteria and beneficial outcomes differed. The RAPID and HEP-COVID trials each required a specified D-dimer elevation for enrollment, but the multiplatform trial did not. Beneficial outcomes ranged from reduction in the primary outcome of organ support-free days without a mortality benefit in the multiplatform trial, to no change in the primary composite outcome of ICU admission, noninvasive or invasive ventilation, or death at Day 28, but a reduction in the secondary outcome of mortality at 28 days in the RAPID trial.[8] The HEP-COVID trial showed improvement in the composite outcome of thrombosis and death. Event rates were significantly higher in HEP-COVID than in the other trials, highlighting the difference in their inclusion criteria. In addition, it should be noted that <20% of screened patients enrolled into the studies; therefore, these findings may not be generalizable to all hospitalized patients with COVID-19.

References

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